Exhibit A

What to expect, how to respond?

("access")

Klinefelter Syndrome (KS) affects 1 in 500 male conceptions and is therefore the most common sex chromosome abnormality. It results in small testes, testosterone deficiency, infertility and often in swelling of glandular breast tissue (gynecomastia). The first report in 9 patients, by HF Klinefelter Jr, EC Reifenstein Jr and F Albright in 1942, was followed by the discovery of an extra X chromosome as the cause of KS by PA Jacobs and JA Strong in 1959. More than two thirds of KS patients have the 47, XXY karyotype, few present with more than 2 X chromosomes or with mosaicism, having a normal XY and another abnormal XXY cell line. Testicular biopsy shows hyalinized and fibrotic seminiferous tubules, with few, if any, areas of sperm production. Seminiferous tubules normally comprise 85% of the testicular volume, and degenerative changes, such as fibrosis and hyalinization of the seminiferous tubules are the cause of testicular atrophy, which is invariably present in KS.

The chromosomal abnormality in KS is caused by an error in the division process in the production of gametes, where sperm or ovum contain an extra X chromosome, in addition to the normal X or Y chromosome. Advanced maternal age may be associated with these division errors in KS.

Whereas a smear of the buccal mucosal membranes can show sex chromatin (Barr bodies), representing the extra X chromosome in KS men, a chromosome analysis, performed in peripheral blood cells will usually confirm the diagnosis of KS, define the number of X chromosomes and provide information about the presence of mosaicism. In the untreated adult KS patient, testosterone levels are usually low or below normal, with elevated LH.

The diagnosis of KS is frequently made by prenatal genetic testing. In infancy the KS boy may present with a small penis, hypospadia or undescended testes. At school-age the child may show behavioral problems or learning disabilities. The adolescent may have tall stature, excessive growth of the lower extremities and delayed puberty, eunuchoidal features and small testes usually remaining at a volume of 2-3 mL. Testosterone production reaches a plateau after age 14 years and may never reach the midnormal adult range, in spite of

high levels of LH stimulation. Adult KS patients have decreased bone mineral density, which could be caused by testosterone deficiency. Many adult KS men are first diagnosed during an infertility evaluation, when testicular atrophy and absence of sperm in the ejaculate are noticed. KS patients have a high incidence of learning disabilities with decreased verbal IQ, but usually normal intellectual performance. Language skills can be impaired, patients may be aggressive, being not inclined to participate in social activities and having a tendency to depression.

Top

KS can be complicated by mild adult-onset diabetes mellitus with insulin resistance, by hypothyroidism, by varicose veins of the lower extremities which can cause venous ulcers, by thinning of the surface of the teeth (taurodontism), which can cause early decay, by breast cancer that may develop in middle age, by leukemia and Hodgkin and non-Hodgkin lymphoma, and in the young by gonadal or extragonadal germinal cell tumors, frequently located in the mediastinum. Cerebrovascular accidents are more common in KS than in men with a normal 46, XY karyotype.

It is desirable to establish the diagnosis of KS as early as possible. This will direct the observation of parents to learning disabilities and behavioral abnormalities, which require remedial action. Attention should be paid to the possibility of complications, and screening tests should be ordered. In adolescence testosterone replacement should be initiated, as soon as gonadotropin levels increase above normal. Testosterone doses must be advanced over years with yearly increments, imitating the increase in testosterone production that occurs during normal puberty. Testosterone not only will advance virilization and support development of adequate bone mineralization, it also can improve fatigue, muscle strength, academic performance and further social adjustment.

Top

In earlier years KS was thought to be invariably associated with antisocial behavior and mental retardation. This impression was prompted by institutionalized patients, whose findings served for earlier reports. Clinical experience with a wider segment of the population and decades of follow-up of KS men provide much more positive information. Early diagnosis, observation and remedial action for emotional and behavioral abnormalities and timely treatment with testosterone can modulate the clinical course of KS and permit patients to live a full life as contributing members of our society.

Wolfram E. Nolten

Editor's Note: Dr. Nolten has given us a broad overview of Klinefelter Syndrome. In the preceding article, he referred to medical, educational, and psychological problems that may be related to this disorder. Dr. Nolten is a founding member of AAKSIS and is also on its Board of Directors.

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Exhibit B

WebMD
Better Information. Better Health.

Article Link: http://men.webmd.com/tc/Klinefelter-Syndrome-Symptoms

men's health

Klinefelter Syndrome - Symptoms

There generally are no signs of Klinefelter syndrome until puberty. At this time, boys with Klinefelter syndrome often do not have the increase in testosterone levels that normally occurs.

Because of low testosterone levels, boys with Klinefelter syndrome may:

- Have sparse pubic, facial, and body hair.
- Have underdeveloped muscles.
- Have enlarged breasts (gynecomastia).
- Be taller than other males in their family and have long legs, narrow shoulders, and wide hips.

Men with Klinefelter syndrome have smaller-than-expected testicles, are generally infertile, and cannot father children without using special fertility techniques.

See an illustration of a male with Klinefelter syndrome.

Mental, emotional, and behavioral concerns

Males with Klinefelter syndrome appear to have reduced abilities in specific areas, including:[1]

- Language development. Boys with Klinefelter syndrome usually have delayed or slowly developing speech skills and poor verbal skills.
- Critical thinking skills, problem solving, and ability to plan.
- Multi-tasking.
- Impulse control.
- Response time.

Boys may have emotional problems that range from being shy and immature to being overly anxious or aggressive. They may also have poor social skills, which may cause problems for them in school and in other social situations. They are at risk for developing psychiatric disorders, such as anxiety, depression, and drug and alcohol abuse.

WebMD Medical Reference from Healthwise healthwise

Last Updated: April 06, 2005

This information is not intended to replace the advice of a doctor.

My Notes:

Klinefelter's syndrome

From Wikipedia, the free encyclopedia

Klinefelter's syndrome
Classification & external resources

ICD-10	Q98.0-Q98.4
ICD-9	758.7

Klinefelter's syndrome, **47XXY** or **XXY syndrome** is a condition caused by a chromosome nondisjunction in males; affected individuals have a pair of X sex chromosomes instead of just one and are at additional risk for some medical conditions. It is named after Dr. Harry Klinefelter, a medical researcher at Massachusetts General Hospital, Boston, Massachusetts, who first described this condition in 1942.[1] The condition exists in roughly 1 out of every 500 males. [2]

Contents

Signs and symptoms

Affected males are almost always sterile, and some degree of language impairment may be present. In adults, possible characteristics vary widely and include little to no signs of affectedness, a lanky, youthful build and facial appearance, or a rounded body type with some degree of gynecomastia (increased breast tissue). Gynecomastia to some extent is present in about a third of individuals affected, a higher percentage than in the XY population. The far end of the spectrum is also associated with an increased risk of breast cancer, pulmonary disease, varicose veins, diabetes mellitus, rheumatoid arthritis, and osteoporosis, risks shared with women.

Rare X-linked recessive problems occur even more infrequently in XXY males, since these conditions are transmitted by genes on the X chromosome, and people with two X chromosomes are typically carriers rather than affected.

There are many variances within the XXY population, just as in the most common 46,XY population. While it is possible to characterise 47,XXY males with certain body types, that in itself should not be the method of identification as to whether someone has 47,XXY or not. The only method of identification is karyotype testing.

Cause

The XXY chromosome arrangement is one of the most common genetic variations from the XY karyotype, occurring in about 1 in 500 live male births. Because of the extra chromosome, individuals with the condition are usually referred to as "XXY Males", or "47,XXY Males" rather than as "suffering

from Klinefelter's syndrome."

In mammals with more than one X chromosome, the genes on all but one X chromosome are barred from being expressed. This happens in XXY males as well as XX females. A few genes, however, have corresponding genes on the Y chromosome and are not barred. These triploid genes in XXY males may be responsible for symptoms associated with Klinefelter's syndrome.

The first published report of a man with a 47,XXY karyotype was by Patricia A. Jacobs and Dr. J.A. Strong at Western General Hospital in Edinburgh, Scotland in 1959.[3] It was found in a 24-year-old man who had signs of Klinefelter syndrome. Dr. Jacobs described her discovery of this first reported human or mammalian chromosome aneuploidy in her 1981 William Allan Memorial Award address.[4]

Treatment

The condition is irreversible, but its symptoms can be altered in a number of ways, including testosterone treatment and other therapies.

While the gender identity of people with XXY karyotype is generally stable, it seems people with Klinefelter's suffer from gender identity disorder more often than people without it. However, this observation is based on the reports of support groups for transgender and transsexual people; no scientific study on this subject has been done. The fact that a person undergoing treatment for gender identity disorder has Klinefelter's syndrome is often missed, or the patient is not told, although in many jurisdictions this additional diagnosis can have legal consequences, for example regarding name change or medical treatment having to be taken.

Inadequately treated hypogonadism in Klinefelter syndrome increases recognized psychosocial morbidity. There is a need for prospectively planned and timed support for young men with Klinefelter syndrome, to ameliorate current poor psychosocial outcomes.[5]

Alternatives to testosterone treatment include a daily regime of cardiovascular exercise along with a complete soy diet or regular vitamins / herbs. Weight bearing exercise creates muscles. [6]

Variations

The 48, XXYY (male) syndrome occurs 1 in 17,000 births and has traditionally been considered to be a variation of Klinefelter's syndrome. XXYY is no longer generally considered a variation of KS, although it has not yet been assigned an ICD-9 code.

Males with Klinefelter syndrome may have a mosaic 47,XXY/46,XY constitutional karyotype and varying degrees of spermatogenic failure. Mosaicism 47,XXY/46,XX with clinical features suggestive of Klinefelter syndrome is very rare. Thus far, only about 10 cases have been described in literature.[7]

References

1. ^ Klinefelter HF Jr, Reifenstein EC Jr, Albright . Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism and increased excretion of follicle-stimulating hormone. *J Clin Endocr Metab* 1942;2:615-624.
2. ^ Klinefelter Syndrome, National Institute of Child Health & Mental Development

3. ^ Jacobs PA, Strong JA. "A case of human intersexuality having a possible XXY sex-determining mechanism". *Nature* 1959 Jan 31;183(4657):302-3. PMID 13632697
4. ^ Jacobs PA. "The William Allan Memorial Award address: human population cytogenetics: the first twenty-five years". *Am J Hum Genet.* 1982 Sep;34(5):689-98. PMID 6751075
5. ^ Simm PJ, Zacharin MR. "The psychosocial impact of Klinefelter syndrome--a 10 year review". *J Pediatr Endocrinol Metab* 2006 Apr;19(4):499-505. PMID 16759035
6. ^ Ivan's Research - http://www.xxytalk.com
7. ^ Velissariou V, Christopoulou S, Karadimas C, Pihos I, Kanaka-Gantenbein C, Kapranos N, Kallipolitis G, Hatzaki A. "Rare XXY/XX mosaicism in a phenotypic male with Klinefelter syndrome: case report". *Eur J Med Genet* 2006 July - August;49(4):331-337. PMID 16829354

See also

- Turner syndrome
- XYY syndrome
- Triple X syndrome
- 48,XXYY syndrome

External links

- National Institute Child Health
- XXYTalk - Global Support Group for Klinefelters Syndrome
- Klinefelter Syndrome & Associates
- American Association for Klinefelter Syndrome Information & Support
- 47xxy.org
- Detailed ICD-9-CM 758.7 data
- klinefeltersyndrome.org
- Austria Klinefelter Syndrom Groupe, Information & Support
- XXYY Syndrome and XXYY Project

Pathology: chromosome abnormalities (Q90-Q99) [hide]

Autosomal trisomies: Down syndrome, Edwards syndrome, Patau syndrome, Trisomy 9, Warkany syndrome 2

Autosomal monosomies/deletions: Wolf-Hirschhorn syndrome, Cri du chat, Angelman syndrome/Prader-Willi Syndrome

X/Y linked: Turner syndrome, Triple X syndrome, **Klinefelter's syndrome**, XYY syndrome

Translocations: Philadelphia chromosome, Burkitt's lymphoma

Categories: Articles with unsourced statements since February 2007 | All articles with unsourced statements | Genetic disorders | Eponymous diseases | Syndromes

Exhibit C

SMH 402
The University of Rochester
Strong Memorial Hospital

RE: DENNIS NELSON
DOB: 3-29-71
SMH#: 119-64-58

CLINICAL NOTE

I had the opportunity to evaluate Dennis Nelson in a follow-up visit on June 14, 1988. Dennis is a 17 year old white male with documented 48,XXXY variant Klinefelter syndrome. Approximately 4 years ago he was started on testosterone replacement and this is being administered through Dr. Romano. He should be getting 250 mg IM Q 3 weeks, but neither Dennis nor his mother are exactly certain of the dose.

The mother tells me that Dennis' behavior has been better since he has been on the testosterone, but he still has significant learning problems, and next year will be entering a job training program. The mother says he has definitely gotten more muscular since he has been on the testosterone, and that he has taken a liking to girls. He likes pictures of girls and has actually had several girlfriends. The mother notes that several days after he gets a shot of testosterone, his behavior is sometimes edgy and more defiant than usual, but this lasts only a short time. Of note is the fact that he started one fire while he was at Hillside 3 years ago while on the testosterone treatment.

On brief physical examination, Dennis is a somewhat defiant teenager who is well developed and muscular. His head circumference is 56.5 cm., weight 151 pounds and height 187 cm. He shows no clinodactyly. Examination of his genitalia shows a normal size phallus with both testes descended but small, measuring about 1.5 x .5 cm.

I reviewed the natural history of XXXY with Dennis' mother and told her that the testosterone therapy would be needed for his entire lifetime. We discussed the fact that this is really replacing the testosterone that his underdeveloped testes are not making. I told the mother that she is doing a very good job in taking care of Dennis, and that a program that would direct Dennis into choosing a vocation would certainly be a reasonable experience for him next year. Dennis will continue to get his IM testosterone shots through Dr. Romano. The mother inquired about starting Dennis on oral testosterone but unfortunately oral testosterone preparations are not availble in the United States although they are available in Europe. If I am able to find out how we can get the oral agents at a reasonable cost, I will notify Dennis' mother.

Marvin E. Miller, M.D.
Associate Professor of Pediatrics
and Genetics

cc: medical records
Dr. Romano

UNIVERSITY OF
ROCHESTER
MEDICAL CENTER

SCHOOL OF MEDICINE AND DENTISTRY
SCHOOL OF NURSING
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ENDOCRINE PRACTICE GROUP

Howard J. Federoff, M.D.
John E. Gench, M.D.
Robert W. Harrison, III, M.D.
Laurence S. Jacobs, M.D.
Steven D. Witchin, M.D.
Paul D. Woolf, M.D.

January 14, 1998

Jose Deperio, M.D.
Wende Correctional Facility
PO Box 1187
Alden, NY 14004-1187

RE: NELSON, Dennis
SMH#: 1196458
DATE SEEN: January 14, 1998

Dear Dr. Deperio:

We had the pleasure of seeing Dennis Nelson in the Endocrine Practice Group. As you know, he is a 26 year old gentleman with a history of Klinefelter's syndrome with his karyotype being XXXY. He was sent to the Endocrine Practice Group for further assessment of the need for testosterone injections. His last injection was in 1993 according to the patient. Since his injections were discontinued, he notes worsening depression and self inflicted injuries. He also notes weight gain and worsened gynecomastia. He has no other complaints. Patient does have a significant history of self inflicted injuries, including multiple bite marks on his arms and chest. Likewise, he has had previous injuries to his neck from nail clippers, according to the patient. Patient also notes that he has a pen injected in his left arm from previous self inflicted injury.

His past medical history is significant for Klinefelter's syndrome, seizure disorder, self inflicted injury, and depression. His current medications include Tegretol 500 mg po bid and Prozac 20 mg po bid.

He has an allergy to Keflex which gives him hives and shortness of breath.

His social history is significant for tobacco use and incarceration since 1991.

His family history is unknown and somewhat non-contributory.

His review of systems was significant for weight gain, approximately 15 pounds, occasional shortness of breath when smoking, but no evidence of constipation, bowel habit changes, chest pain.

Physical examination: His blood pressure was 104/72, heart rate was 48. His weight was 176.7 pounds. Height was 73 cm. His arm span measured approximately 69 cm. His pubis to his head measured approximately 31 cm and his pubis to his feet measured 42 cm. His neck exam revealed no evidence of adenopathy. His thyroid was not enlarged and there were no nodules. His throat was clear without erythema. There was no scleral icterus. His chest was clear without wheezing. His heart was regular without murmurs. He had good peripheral pulses. His abdominal exam

601 Elmwood Avenue, Box 693
Rochester, New York 14642
(716) 275-2901 Fax: (716) 256-2789

was benign, soft, non-tender, non-distended, with no evidence of organomegaly. He did have mild gynecomastia on his chest wall exam. His testes were both distended and were not notably hard and shrunken. They were only mildly small. He did have micro phallice. His skin exam revealed multiple scars with cheloids on his arms, especially on his upper extremities, and there were also lateral neck cheloids as well. Extremities were without edema. He had a mild perioral tremor, otherwise his neurologic exam was non-focal. His extraocular motion was intact without nystagmus and his reflexes were above symmetric and +2.

Assessment: This is a 26 year old gentleman with a history of Klinefelter's syndrome with evidence of decreased testosterone levels both by laboratory reports and by physical examination. Recent endocrine testing revealed both an elevated LH and FSH and a decreased testosterone level. Given his history of depression and gynecomastia, we are recommending that he be restarted on Testosterone injections. He was given a prescription for Testosterone Enanthate 200 mg IM injection every two weeks. He will be followed-up in approximately six months. Today, we will repeat both FSH and LH levels in addition to a free testosterone level. We will update you with any new information.

Thank you very much.

Sincerely,

Mark Ader, M.D.
Resident in Medicine

John E. Gerich, M.D.
Attending in Endocrinology

MA/beh